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REVIEW ARTICLE

Triple Antithrombotic Therapy *vs.* Double Antithrombotic Therapy: One Scenario, 8 Questions, Many Conclusions

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Abstract: In patients with atrial fibrillation undergoing percutaneous coronary intervention with the placement of stents, a triple antithrombotic therapy is empirically established, which consists of a combination of dual antithrombotic therapy (aspirin plus a P2Y12 inhibitor) and an oral anticoagulant agent. This choice is guided by the desirable result of reducing cerebrovascular and coronary ischemic events. However, there is an unwelcome outcome: an increased incidence of bleeding. On this matter, in 2018, a North American Perspective Update was published, about a year later it was followed by the publication of the European focus update on the dual antiplatelet therapy. After analysing the main differences between these two consensus documents, this review aims at examining the major studies on which they are based on, as a starting point to define the foundation of new trials that can help shed light on this prominent topic.

Keywords: Triple antithrombotic therapy, dual antithrombotic therapy, atrial fibrillation, Percutaneous Coronary Intervention (PCI), NOAC, OAC.

1. INTRODUCTION

1.1. The Scenario

Approximately 5 to 8% of patients who undergo percutaneous coronary intervention (PCI) have atrial fibrillation (AF) [1]. In this subset of patients, the management of this arrhythmia becomes particularly challenging.

Oral anticoagulation (OAC) therapy is recommended in patients with AF for primary and secondary stroke and systemic embolism prevention, while Dual AntiPlatelet Therapy (DAPT: Aspirin plus a P2Y12 inhibitor) is recommended in patients who are undergoing PCI with stent implantation in order to avoid thrombotic complications. Therefore, in clinical practice, the use of Triple Antithrombotic Therapy (TT), which consists of an OAC combined with DAPT, has been empirically used after PCI in patients with AF requiring OAC therapy, with the belief that the administration of three drugs may minimize the risk of cerebrovascular and coronary ischemic events. In the meantime, this strategy is responsible for an increased incidence of hemorrhage.

Thus patients treated with TT should be considered at high risk of bleeding, hinting the need to implement strategies to minimize this possibility. In this scenario, the identification of an antithrombotic regimen with a better risk/benefit ratio is highly desirable.

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1.2. What is new about Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention?

Recently, a North American Perspective–2018 Update was published [2]. In comparison with the previous 2016 Update, the key changes are [3]:

- A non–vitamin K antagonist oral anticoagulant (NOAC) should be preferred over a vitamin K antagonist (VKA) unless it is contraindicated.
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
- A double-therapy regimen (Oral Anticoagulant plus single antiplatelet therapy with a $P2Y1_2$ inhibitor) by the time of hospital discharge might be reasonable for most patients.

1.3. What are the main differences between European [4] and North American consensus documents/guidelines [2]?

Summary of key changes between 2016 and 2018 Expert consensus on antithrombotic management of patients with AF undergoing PCI (Table **1**).

1.4. What is the main cohort study that investigated this issue?

The Danish nationwide cohort study [5], which selected patients with AF admitted for Myocardial Infarction (MI) or for PCI between January 2001 and December 2009.

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Table 1. Summary of Key Changes Between 2016 and 2018 Expert Consensus on Antithrombotic Management of Patients With AF Undergoing PCI.

	North American Perspective–2018 Update [2]	2017 ESC Focused Update on Dual Antiplatelet Therapy [4]
Choice of Anticoagulant	A NOAC (rather than a VKA) should be generally preferred in most patients unless contraindicated.	There is no preference between VKA and NOAC.
Choice of $P2Y_{12}$ inhibitor	Clopidogrel is the P2Y12 inhibitor of choice. Ticagrelor may represent a reasonable treatment option in selected patients. Plasugrel should be avoided.	Clopidogrel is the only $P2Y_{12}$ inhibitor approved. Plasugrel and Ticagrelor should be avoided.
Strategy (double *vs.* triple therapy)	A double-therapy regimen (OAC plus P2Y12 inhibitor) immediately after hospital discharge should be considered for most patients. Extending the use of aspirin beyond hospital discharge should be considered only for selected patients (high ischemic/thrombotic and low bleeding risks) and for a limited period of time (*eg*, 1 mo).	Triple therapy with aspirin, clopidogrel, and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic (*e.g*. Acute Coronary Syndrome or elective Percutaneous Coronary Intervention (PCI) with other anatomical/procedural characteristics that outweigh the bleeding risk. Dual therapy with clopidogrel 75 mg/day and OAC should be considered in patients in whom the bleeding risk outweighs the ischaemic risk.

AF indicates atrial fibrillation; PCI, percutaneous coronary intervention; NOAC indicates non–vitamin K antagonist oral anticoagulant;, OAC, oral anticoagulation; VKA, vitamin K antagonist.

1.5. What are the main randomized trials on which the guidelines are based?

The main trials are: the WOEST trial [6], the ISAR-TRIPLE trial [7], the PIONEER AF-PCI trial and the RE-DUAL PCI trial [8].

1.6. Is AF the only indication for OAC therapy regarding the examined populations?

The answer is positive only for the RE-DUAL PCI trial [8] and the PIONEER AF-PCI trial [1]. However, AF was the predominant indication for OAC in the WOEST trial [6] (approximately 70% of the patients) and in the ISAR-TRIPLE trial [7] (approximately 86% of the patients).

1.7. Which investigations have provided accurate angiographic characteristics according to treated lesions?

Only the WOEST trial [6] and the ISAR-Triple trial [7] presented detailed angiographic characteristics.

1.8. Is there a discrepancy of the mean CHADSVASC / CHA_2DS_2VASC-score regarding the populations examined in these different investigations?

Yes, there is. Considering the patients on TT, in the WOEST Trial [6] a CHA_2DS_2-VASC score of 2 and 3 was reported for the 26% and 36% of the study population, respectively.

Considering the same scores, in the ISAR-TRIPLE trial [7], 6,9% and 16,1% of the population showed, respectively, a score of 2 and 3. Finally, in the PIONEER AF-PCI [1], the same scores were reported for 13% and 21% of the population respectively.

Regarding the RE-DUAL PCI trial [8], the percentage of patients for each CHA_2DS_2-VASC score was not stated, but it was attested that the mean score varied from 3.3 ±1.5 to 3.8 ±1.5. Moreover, with reference to the patients on TT, the score was <2 for 184 subjects (24.1 %) and >2 for 580 subjects (75.9%) of the examined population.

Finally, in the DANISH COHORT [5] the reported mean $CHADS_2$ score was 1,5 (SD 1.5). Of note, 36,9% of the entire population had a score of 0 or 1.

1.9. Which type of Bleeding Classifications was adopted in these studies?

- The WOEST Trial [6]: TIMI, GUSTO and BARC
- The ISAR-TRIPLE trial [7]: TIMI
- The PIONEER AF-PCI trial [1]: TIMI
- The RE-DUAL PCI trial [8]: ISTH and TIMI
- The DANISH COHORT [5]: it was not adopted as an international classification. However, bleeding was recorded as nonfatal or as fatal, which was defined as either first admission with a diagnosis of nonfatal bleeding registered at discharge or as death from bleeding identified through the National Causes of Death Register.

TIMI = Thrombolysis In Myocardial Infarction; GUSTO = Global Utilization Of Streptokinase And TPA For Occluded Arteries; BARC = Bleeding Academic Research Consortium; ISTH = International Society on Thrombosis and Hemostasis.

Summary of the main investigations concerning Triple Antithrombotic Therapy. (Tables **2** and **3**).

Table 2. Summary of the main investigations concerning Triple antithrombotic therapy.

Abbreviation for the Investigation, Journal and Year	N° Patients	Indication for PCI/OAC	Primary End Point	Secondary Endpoint	Treatment Arms	SDF
Danish Nation-wide cohort study [5] Circulation 2012	11480	ACS† 76,4% AF‡ 100%	Bleedings not defined by an international classification , but classified as nonfatal or fatal.	Cardiovascular death or death from ischemic stroke, nonfatal MI‖, or nonfatal ischemic stroke.	Subjects diagnosed with AF‡ who had been hospitalized for MI‖ (n=13,970) or PCI* (n=2,909). According to antithrombotic regimen 7 Groups identified: 1) Asprin = 3388 2) Clopidogrel = 768 3) VKA = 848 4) Aspirin + Clopidogrel = 3144 5) Aspirin + VKA = 1310 6) Clopidogrel + VKA = 527 7) Aspirin + Clopidogrel + VKA = 1495	
Woest Trial [6] Lancet 2013	573	ACS† 25-30% AF‡ 69%	Any bleeding in patients taking OAC§ and undergoing PCI*.	Death, MI‖, stroke, target-vessel revascularization stent thrombosis	Clopidogrel alone (double therapy) or clopidogrel and aspirin (triple therapy) for at least 1 month, up to 1 year at the discretion of the attending physician, in patients who received a bare metal stent for stable coronary disease. In patients with acute coronary syndromes or who received drug-eluting stents, clopidogrel was administered for at least 1 year.	
Isar-triple trial [7] jacc 2015	614	ACS† 31%-33,3% AF‡ 82,7%-85%	Composite of death, MI‖, stent thrombosis, stroke, or TIMI** major bleeding	Ischemic complications (cumulative incidence of cardiac death, MI‖, stent thrombosis, stroke) or bleeding complications (TIMI** major bleeding)	In patient receiving concomitant aspirin and OAC§, 6-week *vs* a 6-month clopidogrel Treatment Regimen,	
Pioneer AF-PCI trial [1] nejm 2016	2124	ACS† 51,5%-53,2% AF‡ 100%	Any clinically significant bleeding	CV# death, MI‖, stroke	Group 1) Warfarin with ASA§§ and P2Y12 inhibitor ‖‖ Group 2) Rivaroxaban 2.5 mg twice daily with ASA§§ and P2Y12 inhibitor‖‖ Group 3) Rivaroxaban 15 mg daily ## and P2Y12 inhibitor‖‖	
Re-dual Pci trial [8] Nejm 2017	2725	ACS† 48,3%-51,9% AF‡ 100%	ISTH ††major or clinically relevant nonmajor bleeding	Death, MI‖, stroke, SE‡‡, or unplanned revascularization	Group 1) Warfarin with ASA§§*** and P2Y12 inhibitor††† Group 2) Dabigatran 110 mg twice daily and P2Y12 inhibitor††† Group 3) Dabigatran 150 mg‡‡‡ twice daily and P2Y12 inhibitor†††	

PCI* = Percutaneous coronary intervention**; ACS**† = Acute coronary syndrome**; AF**‡ = Atrial Fibrillation**; OAC**§ = Oral Anticoagulant; **MI**‖ = Myorcardial infarction; **CV**# = Cardiovascular; **TIMI**** = Thrombolysis in Myocardial Infarction; **ISTH**†† = International society on thrombosis and haemostasis; **SE** ‡‡ = Systemic embolism; **ASA** §§ = acetylsalicylic acid.

‖‖Clopidogrel, prasugrel, or ticagrelor; clopidogrel was used in 94% of the enrolled population.

##Rivaroxaban 10 mg daily if CrCl was 30 to 50 mL/min.

***Aspirin discontinued at 1 month (bare metal stents) or at 3 months (DES).

†††Clopidogrel or ticagrelor; ticagrelor was prescribed in 12% of enrolled patients.

‡‡‡Patients >80 years of age outside of the United States were randomized to only warfarin or dabigatran 110 mg twice daily.

Table 3. Summary of the main investigations concerning Triple antithrombotic therapy.

Abbreviation for the Investigation, Journal and Year	N° Patients	Objective	Outcomes	SDF
Danish Nationwide cohort study [5] Circulation 2012	11480	Retrospective cohort	Primary outcome was nonfatal or fatal bleeding defined as either first admission with a diagnosis of nonfatal bleeding registered at discharge or as death from bleeding Secondary outcome: MACE*.	
Woest Trial [6] Lancet 2013	573	Superiority	The trial was only powered to assess whether clopidogrel alone was better than clopidogrel and aspirin in the prevention of bleeding. Significant differences in favour of the double-therapy group were seen only for mild and moderate bleeding.	
isar-triple trial [7] jacc 2015	614	Superiority	Trial not powered to detect differences in the individual components of the primary endpoint	
Pioneer AF-PCI trial [1] nejm 2016	2124	Non inferiority	The trial was not powered to definitively establish either superiority or noninferiority. Surprisingly, it has been shown a very low rate of stent thrombosis (0.8%) in group 1 (no DAPT†) and, at the same time, a relatively low rate of stroke in group 2 (1.4% of - patients treated with rivaroxaban 2,5 twice daily. Moreover, 12.8% of patients had a $CHADS_2$ score of 0 points, and 1% of them had a CHA_2DS_2Vasc of 0 points. Of note, great CI‡regarding MACE*: Stroke (0,39-2,96). Stent Thrombosis (0,32-4,45); Death from Cardiovascular causes (0,59-2,8).	
Re-dual Pci trial [8] Nejm 2017	2725	Non inferiority	Different regimens of full-dose anticoagulation therapy with dabigatran (either 110 mg or 150 mg twice daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) resulted in a lower risk of major or clinically relevant nonmajor bleeding events than the risk with triple therapy with warfarin; in addition, dual therapy with dabigatran was noninferior to triple therapy with warfarin with respect to the composite efficacy endpoint of thromboembolic events, death, or unplanned revascularization.	

MACE* = major adverse cardiac events; **DAPT†** = Dual antiplatelet therapy; **CI‡** = Confidence Interval;

CONCLUSION

The current medical treatment adopted for this subset of patients is based on non-homogenous evidence.

Our knowledge is based predominantly on relatively small (WOEST and ISAR) [6, 7] or big (PIONEER and RE-DUAL) [1, 8] trials but with an objective of non-inferiority and a sample size derived from an end-point of bleeding.

Nevertheless, the trials mentioned above have represented an important starting point to define the best therapeutic approach between TT and dual therapy (OAC plus clopidogrel) in patients with AF undergoing PCI. Despite the univocal conclusion that patients on TT have more bleeding, these studies have shown some weak points that could guide the design of new trials. It is important to describe the angiographic characteristics of each patient, to take into consideration the number of the implanted stents, and where they were implanted, in order to define the presence of high-risk features of stent-driven recurrent ischaemic events.

It would also be interesting to test the risk/benefit ratio of TT avoiding the use of both Prasugrel and Ticagrelor and shortening its duration from twelve months to a maximum of six months based on the patient's individual risk, in accordance with the current European guidelines [4].

Moreover, these studies have highlighted some controversies about the risk/benefit ratio of MACE / Major Bleeding of this approach. However, the great Confidence Intervals shown in the biggest trials (PIONEER AND RE-DUAL) [6, 7] about the single components of MACE suggest major efforts in terms of large double-blind, randomized clinical trials in order to shed light on this critical topic.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Gibson CM, Mehran R, Bode C, *et al*. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016; 375(25): 2423-34.

[2] Angiolillo DJ, Goodman SG, Bhatt DL *et al*. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention a North American perspective–2018 update. Circulation 2018; 138: 527-36.

[3] Angiolillo DJ, Goodman SG, Bhatt DL, *et al*. Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A North American Perspective-2016 Update. Circ Cardiovasc Interv 2016; 9(11). pii: e004395.

[4] Valgimigli M, Bueno H, Byrne RA, *et al.* ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39(3): 213-60.

[5] Lamberts M, Olesen JB, Ruwald MH, *et al*. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: A nationwide cohort study. Circulation 2012; 126(10): 1185-93.

[6] Dewilde WJ, Oirbans T, Verheugt FW, *et al.* WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013; 381(9872): 1107-15.

[7] Fiedler KA, Maeng M, Mehilli J, *et al*. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: The ISAR-TRIPLE trial. J Am Coll Cardiol 2015; 65(16): 1619-29.

[8] Cannon CP, Bhatt DL, Oldgren J, *et al.* RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017; 377(16): 1513-24.